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The Action of Bromine on Meta-Acetyl-Anisidine

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THE ACTION OF BROMINE ON META-ACETYL-ANISIDINE

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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ENTITLED THE ACTION OF BROMINE ON META-ACETYL-ANISIDINE

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

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THE ACTION OF BROMINE ON META*ACETYL*ANISIDINE.

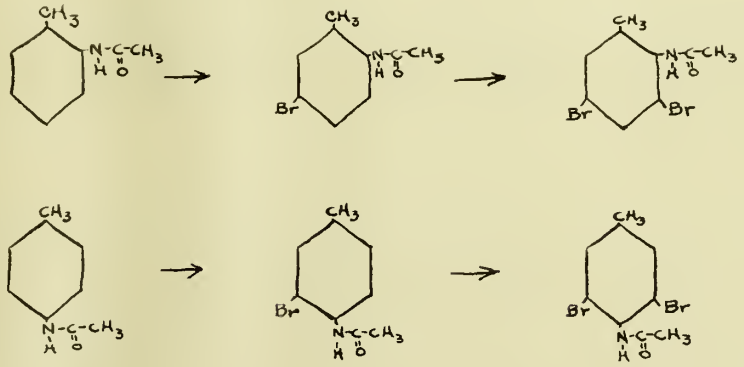
INTRODUCTION.

In 1895, E. Vaubel[1] obtained, by the direct bromination of phenacetine, a brown oily liquid which he was unable to crystallize and which he took to be 1-methoxy, 3-brom, 4-acetamino benzene as described by Steadel[2]. Two years later[3], he published the results of further investigation upon the same compound, but took a different view as to the position taken by the bromine, placing it ertho to the amino group instead of to the methoxyl. The pure substance was obtained as a white solid melting at 20°. This view of the structure was upheld by work done in connection with the patent taken out by Hofmann and Schötensack[4] as well as by experiments on certain anisole derivatives and hydrochinonmonomethyl ethers mentioned in the same article.

The exact mechanism of the halogenation of the anilines was taken up in 1899 by Chattaway[5], who advanced the theory that all halogens first attacked the amino group and then, by a re-arrangement, entered the ring, while the replaced hydrogen migrated to the nitrogen. In this change, the position taken by the halogen would be governed by the orientating influence of the amino group alone, and not affected by any other substituent. Definite evidence of such an actual re-arrangement was first recorded by Bender[6], in 1886, when he isolated $C_6H_5NCl\cdot COCH_3$ and noticed a rather

violent re-arrangement to p-$ClC_6H_4NHCOCH_3$ in the cold with concentrated HCl, and on the water bath with alcohol.

Chattaway, working in conjunction with Orton[7], obtained further proof of his theory and published a series of papers in 1900 in which he gave the results of his investigations upon the disubstitution products and the quantitative yields of the various monosubstitution products of the toluides. It is interesting to note that the ease with which the re-arrangement of a nitrogen halide is effected is proportional to the ease of the direct formation of the latter product. The action of bromine on ortho and para acetyl-toluidides was found to be:



, the bromine entering either the ortho or para position to the amino group in each case. The treatment of the anilides with chlorine gave about 95 percent of the p-chloro and 5 percent of the o-chloro compound, with none of the m-chloro.

In the light of the above work by Chattaway who seems to have established his theory by extended investigation, it seems that bromine, in acting on meta-acetyl-anisidine (1-methoxy,3-acetamino,benzene), could take either position four, ortho to the amino group, or six, para to the amino

group. If it took the former place, the product should be the same as that obtained from para-anisidine through the series:

If, on the other hand, it took the position para to the amino group, the resulting product should be the same as that obtained from ortho-anisidine through the series:

An investigation of the first series is taken up in this paper, while the second series is being studied by Mr. R.A.Nelson at the University of Illinois. The investigation of the second series presents some difficulties due to the production of two nitro compounds which must be separated by fractional crystallization, and whose composition does not seem to have been thoroughly established. This matter has been investigated by the direct bromination of para-anisidine, and by the bromination and reduction of para-nitranisole, which should give identical products. The results of this work are reported in this paper.

EXPERIMENTAL.

The meta-acetyl-anisidine used in this work was prepared according to the directions found in the thesis of Huang Chen, University of Illinois, 1913.

Bromo-meta-acetyl-anisidine.

Twelve grams of the m-acetyl-anisidine were dissolved in 40 cc. of glacial acetic acid, cooled with ice water, and treated with 12 grams of bromine (C.P.), dissolved in 40 cc. of glacial acetic acid. When the bromine had all been added, the mixture, from which the product had begun to crystallize, was poured into 500 cc. of water. The white, crystalline product was dissolved in hot alcohol, treated with bone-black, and filtered. After the addition of hot water sufficient to produce a faint, permanent turbidity, the product separated in the form of white needles having a melting point of 157°. This bromo-m-acetyl-anisidine is insoluble in water; slightly soluble in alcohol or ligroin; fairly soluble in cold benzene; and readily soluble in chloroform or hot benzene.

Bromo-meta-anisidine.

Twenty-two grams of the bromo-m--acetyl-anisidine were dissolved in 50 cc. of hot alcohol and 25 cc. oc concentrated HCl added through the condenser. The mixture was boiled gently for an hour when the reaction was complete.

Upon cooling, the hydrochloride of the base separated.

Water was added to dissolve the hydrochloride and the solution evaporated on the water bath to remove the alcohol and acetic ester. After filtration, the solution was diluted and made alkaline with NaOH when the base separated from the hot solution as an oil which crystallized in needles upon cooling. The yield of the crude product was 17 grams, or 90 percent of the theoretical. When recrystallized from dilute alcohol, the base was obtained as white needles with a melting point of 98°.

Combustions of the base gave the following percentages of nitrogen; 5.94 , 6.7, while the theoretical percent is 5.73 .

A portion of the hydrochloride was titrated with standard NaOH.

Weight of hydrochloride ---------- 0.2502 grams

Cc. of 0.1115N NaOH (under end-point)-- 9.175
(past end-point)-- 9.275

Theoretical weight of HCl for C_7H_9ONCl --- 0.03848 grams

Found weight of HCl ---------- 0.03846 grams.

The hydrochloride decomposed at 197°.

Para-acetyl-anisidine[8]

Fifty grams of para- anisidine and 5 grams of anhydrous sodium acetate were dissolved in 100 cc. of glacial acetic acid, and 50 grams of acetic anhydride slowly added. After standing a few moments, the solution was poured into 500 cc. of cold water when the white crystalline product separated out. This was filtered and dried on a porous plate. Melting

point was I27°-I28°, and the yield was 56 grams, or 84 percent of the theoretical.

Meta-nitro-para-acetyl-anisidine.

This compound was prepared by Reverdin[9] in I896 by direct nitration. Fourteen grams of HNO_3 (S.G. I.48) were added to 30 grams of p-acetyl-anisidine dissolved in I00 cc. of cold glacial acetic acid. To the clear, red solution were added 300 cc. of hot water. The orange colored crystals of the nitro compound which were precipitated had a melting point of II8°-II9°, after being dried on a plate. The yield was 3I grams, or 8I percent of the theoretical. Reverdin obtained a melting point of II7° while Hähle[10] obtained only II5° in his work on nitro-amido-phenol-tetramethylammonium.

Meta-nitro-para-anisidine[11].

Thirty-one grams of the above nitro compound were dissolved in I29 cc. of alcohol with slight heating, and I7.2 grams of KOH dissolved in 35.8 cc. of water added. The yellow solution changed to a red solution which was heated on a water bath for 30 minutes. Upon cooling, a bright red, granular product separated, which was filtered off and dried. The melting point was I25°-I26°, and the yield was 23 grams, or 94 percent of the theoretical.

Meta-nitro-para-bromo-anisole.

This was prepared according to the method used by F. Ullmann[12] in the case of nitro aniline.

Eighteen and three-tenths grams of the m-nitro-p-anisidine were dissolved in 22.5 grams of concentrated H_2SO_4 and the mixture, which had become hot from the reaction, poured over 125 grams of ice. Seven and a half grams of $NaNO_2$, dissolved in 25 cc. of water, were then introduced into the bottom of the solution through a pipette, used as a stirring rod. The clear solution of the diazonium compound was poured through a funnel into the Cu_2Br_2 solution prepared by mixing 14.5grams $CuSO_4$, 100 grams H_2O, 37.5 grams NaBr, and 3.5 grams of copper bronze, and heating to 40° until the solution had become colorless. As attempts to distill with steam gave but poor results, the solution was extracted with ether and dried over fused calcium chloride. Upon evaporation of the ether, a light yellow mobile liquid was obtained which turned brown on standing. This was frozen in a mixture of HCl and ice, and pressed out on a plate giving a faintly yellow solid melting at 31°-32°.

Better results were obtained by dissolving the base in HBr instead of in H_2SO_4, using the same procedure and equivalent amounts of the substances. A reddish-brown, mobile liquid resulted which was at once reduced.

Meta-amino-para-bromo-anisole.

The nitro-bromo-anisole prepared above was reduced by heating on the water bath for several hours a mixture of 4.5 grams of the anisole, 13.5 grams of $SnCl_2$, and 30 cc. of HCl. The red liquid slowly disappeared, and upon cooling, grey crystals of the double salt of tin separated. These were

filtered off, dissolved in 200 cc. of water with a little HCl, and the tin precipitated with H_2S. The tin sulphides were filtered off, the solution evaporated to dryness, the residue dissolved in water, the solution made alkaline with KOH and extracted with ether. The latter was evaporated off, leaving the base as a brown, oily liquid.

Meta-acetamino-para-bromo-anisole.

The above base was dissolved in acetic acid and treated with acetic anhydride, and poured into water. As the acetyl compound did not separate, the solution was evaporated to 15-20 cc. and neutralized with Na_2CO_3 when a brown oil, lighter than water, separated which solidified after standing some time. This was recrystallized from a very little dilute alcohol, the liquid which separated at first solidifying upon standing over night. The solid was dried on a porous plate and a melting point of 72°-73° obtained.

As there does not seem to be any doubt as to the positions taken by the substituents in the above series, and as the compound does not agree in melting point with that obtained by the direct bromination of the p-anisidine, it is probable that the bromine enters in the position ortho to the methoxy group and para to the amino group.

Mr. Nelson nitrated o-anisidine and substituted bromine for the amino group by the diazonium reaction. By subsequent reduction, he obtained a base which melted at 98° and agreed very well with that obtained by the direct bromination of the m-acetyl-anisidine, but the acetyl derivative

of his substance had a melting point of 134° instead of 137° as would be expected from the preceding results. Since the only questionable part of his work was in the position taken by the nitro group, this matter was investigated through attempts to compare the substance obtained through the bromination of p-anisidine with the compound obtained by the bromination and subsequent reduction of p-nitranisole.

Bromo-acetyl-para- anisidine.[14]

Ten grams of bromine were dissolved in 35 cc. of glacial acetic acid and added to 10 grams of acet-p-anisidine dissolved in 35 cc. of glacial acetic acid, the mixture being kept cool with ice water. The reddish solution was poured into 500 cc. of water, when a slightly colored solid separated which was filtered and recrystallized from dilute alcohol. The white crystalline product was dried on a plate and, after a second crystallization, gave a melting point of 113°-114°.

Bromo-para-anisidine.[14]

The acetyl group of the above compound was eliminated in the same manner as that of the bromo-m-acetyl-anisidine, page 4. The brown, crystalline product was recrystallized from dilute alcohol, and gave a melting point of 62°-63°.

Ortho-bromo-para-nitranisole.

This compound was prepared by the method used by Wheeler and Mac Farland[15] in brominating nitrobenzene. Thirty-seven and three-tenths grams of p-nitranisole with 3grams of iron

were heated to 130° under a reflux condenser and 60 grams of bromine slowly added during three quarters of an hour. After an additional three quarters of an hour's heating, water was added to the dark brown mass and 15 grams of $NaHSO_3$ to remove the excess of bromine and ferric bromide. Steam was tried as a means of getting the pure product, but no results were obtained, so the mass was pressed out on a porous plate giving a brownish-grey substance. The yield was about eighty percent of the theoretical. After several recrystallizations from hot alcohol without water, and treatment with bone-black, a melting point of 140°-141° was obtained. The substance is slightly soluble in water, and easily soluble in alcohol or benzene. It was analysed by a modified Volhard method[16] giving 33.0 and 31.1 percents of bromine, the theoretical being 32.78 percent of bromine.

A peculiarity of this substance is that, although it is a white solid, its solutions in ligroin, benzene, alcohol, or water are yellow and stain the skin yellow. Hantzsch[17] has explained this color effect as due to a wandering of the methyl group in accordance with the following scheme:

It is very likely that the equilibrium in such a system would be shifted in favor of the colored compound by the presence of a bromine atom in a position ortho to the methoxyl.

II.

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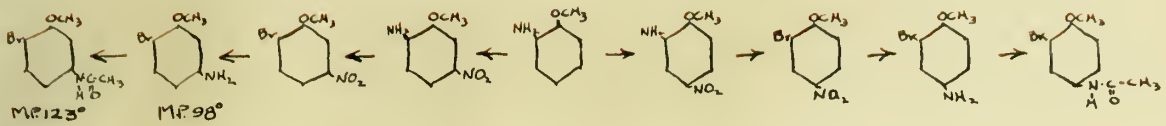

Work of Mr. R. A. Nelson.